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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Han Htun and Gordon L. Hager	**Examiner:**	Bradley L. Sisson, Ph.D.
Serial No.:	10/001,486	**Group Art Unit:**	1634
Filed:	November 15, 2001	**Docket:**	30426.1USD1
Title:	METHODS FOR SCREENING LIGANDS THAT ACTIVATE THE TRANSLOCATION OF A STEROID RECEPTOR TO THE NUCLEUS IN MAMMALIAN CELLS		

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this Transmittal Letter and the paper, as described hereinabove, are being deposited in the United States Postal Service, as first class mail, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on March 19, 2007.

By: _____
Richelle Ann Domingo

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

We are transmitting herewith the attached:

☒ Transmittal Sheet in triplicate containing Certificate of Mailing under 37 CFR §1.8
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Pasadena, California 91101
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SIR:

APPEAL BRIEF AND PETITION FOR FOUR-MONTH EXTENSION OF TIME

Applicants hereby appeal to the Board of Patent Appeals and Interferences ("the Board") of the United States Patent and Trademark Office ("the Office") from the final Office Action issued May 18, 2006. Applicants filed a response to the Office Action with one-month extension of time on September 18, 2006. Applicants filed a Notice of Appeal on September 18, 2006 with the proper fee. The Office issued an Advisory Action dated October 12, 2006. An Appeal Brief was due November 18, 2006. A four month extension of time for filing the Appeal Brief is hereby requested. The fee under 37 C.F.R. §41.20(b)(2) for $250.00 for filing a Brief in support of an appeal, and the fee under 37 C.F.R. §1.17(a)(4) for $795.00 for a four month extension of time to file the Brief, for a total of $1045.00, is due. A check in the amount of $1045.00 is enclosed. An Appeal Brief is now due March 18, 2007. However, since March 18, fell on a Sunday, a response filed the next business day namely, Monday, March 19, 2007, is considered timely. Therefore, this Appeal Brief is timely filed.

This Appeal Brief is being submitted in triplicate, as required under 37 C.F.R. §1.192(a).

1. REAL PARTY IN INTEREST

The parties named in the caption are the inventors of the claimed methods. Further, the assignee of record of the subject application is Han Htun and The Government of the United States of America as represented by The Secretary of the Department of Health and Human Services c/o National Institute of Health.

2. RELATED APPEALS AND INTERFERENCES

At the present time there are no pending appeals or interferences related to this case.

3. STATUS OF CLAIMS

Claims 1-15 and 19-58 have been cancelled. Claims 16-17 are pending and have been rejected by the Examiner.

Only claim 18 has been allowed.

4. STATUS OF AMENDMENTS

Claim 18 has been allowed. Claims 16 and 17 are being examined and a copy of the claims is provided as Appendix A.

5. SUMMARY OF THE INVENTION

Applicants' invention involves a method of screening for a ligand that activates the translocation of a steroid receptor to the nucleus in a mammalian cell comprising (a) contacting a mammalian cell having a nucleus with the ligand, wherein the cell has a plurality of steroid receptor response elements, wherein the steroid receptor response elements comprise a plurality of AGAACA (SEQ ID NO:4) or AGGTCA (SEQ ID NO:5), in an array such that the response element can be directly detected when bound by fluorescently labeled steroid receptor; and (b) detecting the location of fluorescence within the cell, a change in the relative fluorescence of the nucleus to the cytoplasm so as to increase the fluorescence of the nucleus indicating a ligand that activates the translocation of a steroid receptor to the nucleus in a mammalian cell.

Additionally, the invention also includes a method of screening for a ligand that activates the translocation of a steroid receptor to the nucleus in a mammalian cell comprising (a) contacting a mammalian cell having a nucleus with the ligand, wherein the cell has a plurality of steroid receptor response elements, wherein the steroid receptor response elements comprise a plurality of AGAACA (SEQ ID NO:4) or AGGTCA (SEQ ID NO:5), in an array such that the response element can be directly detected when bound by fluorescently labeled steroid receptor; and (b) detecting the location of fluorescence within the cell, a change in the relative fluorescence of the nucleus to the cytoplasm so as to increase the fluorescence of the nucleus indicating a ligand that activates the translocation of a steroid receptor to the nucleus in a mammalian cell, wherein the mammalian cell is a cell of the cell line designated 3134 deposited with American Type Culture Collection under accession number CRL-11998 (ATCC).

6. ISSUES

The only remaining rejection is under 35 U.S.C. §112, first paragraph. Specifically, the Office asserts that the specification fails to provide an adequate description of: 1) "other cell lines" which can be used for the invention i.e., the specification allegedly does not provide adequate written description for the "genus" of cells (mammalian cells with a plurality of steroid receptor response elements) encompassed by the claims, and 2) how such cells are to be used for the invention.

7. GROUPING OF THE CLAIMS

Claims 16-18 are not separately patentable from each other, and the rejected claims stand or fall together.

8. ARGUMENTS

Adequate Written Description for a "Genus" of Mammalian Cells with Multiple Steroid Receptor Response Elements

35 U.S.C. §112 requires that, "the specification contain a written description of **the invention**, and ... enable any person skilled in the art to which it pertains, to make and use the **same** ..." (emphasis added). One is not required to enable any more than what is claimed.

The specification complies with 35 U.S.C. §112 because it provides adequate written description for the "genus" of cells required by the claims (i.e., a mammalian cell that has a plurality of steroid response elements) for the following reasons.

First, the specification as originally filed discloses actual enabling experiments embodying the claimed methods. Specifically, the application discloses cell lines with multiple steroid response elements: 3134 cells (in the specification at page 51, line 21 to page 56, line 7; Figures 1-2); 1471.1 cells (in the specification at page 39, lines 23-30; page 18, lines 4-7; Figure 3C) and 3677 cells (in the specification at page 40, lines 1-6; page 18, lines 4-7).

Second, Applicants have disclosed the requisite starting materials and the use thereof needed to practice the full scope of the invention e.g., Applicants have disclosed the type of cells that can be used as starting materials for the present invention (in the specification at page 16, lines 15-31; page 24, lines 21-29). In detail, the specification discloses that "any cell can be utilized, since the resulting location of fluorescence can be visualized as either in the cytoplasm or in the nucleus" (in the specification at page 15, lines 19-20). Further the specification describes that "additionally, for such detection events, cells having increased copy number of the binding site, in an array, can be used" (in the specification at page 15, lines 20-21). Therefore, the present specification clearly teaches that any mammalian cell having a plurality of steroid response elements in an array such that the element can be directly detected can be used to perform the screening for a ligand that activates the translocation of the steroid receptor to the nucleus. By a plurality of steroid response elements is meant that the number of copies of the elements is greater than one (in the specification at page 17, lines 13-23). It has been known for higher eukaryotic genomes to contain naturally occuring repetitive sequences (in the specification at page 61, lines 26-28). Therefore, any mammalian cell which meets these criteria can by used as a starting material for the present invention.

Additionally, the specification describes the localizations of the elements to be "in sufficiently close physical proximity along a chromosome, either present endogenously or artificially introduced or induced, or in extrachromosomally replicating episomes" (in the specification at page 17, lines 3-5; page 19, lines 1-2). Methods for artificially

introducing or inducing a gene into chromosomes are well known in the art (Sambrook et al., *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor Laboratory Press 1989); Kriegler M. *Gene Transfer and Expression: A Laboratory Manual* (W. H. Freeman and Co, New York, N.Y., 1993), as are transformation or transfection methods for extrachromosomally replicating episomes. Nevertheless, examples for these methods are given in the specification of the invention (e.g. page 40, lines 8-18). A non-limiting example of an artificially modified cell including a high number of copies of the response elements is the cell line 3134 which is described in the application in detail and which is deposited with American Type Culture Collection as accession number CRL-11998 (ATTC) (e.g. in the specification at page 17, lines 22-24). This cell line is particularly useful for detection of ligands. The same results can be achieved by the use of any desired (naturally occurring or artificially modified) mammal cell having a plurality of steroid response elements in such an array; as stated above.

Third, Applicants have disclosed how to prepare additional cell lines containing receptor response elements. Methods to prepare human and other mammalian cell lines containing receptor response elements are disclosed (in the specification at page 57, lines 19 to page 58, line 3) with a detailed step-by-step protocol (in the specification at page 58, lines 5 to page 63, line 13).

Therefore, in view of the reasons stated above, Applicants have provided adequate written disclosure to encompass the scope of the claims e.g., there is adequate written description for the genus of a mammalian cell that has a plurality of steroid response elements.

Adequate Written Description for Use of Any Mammalian Cell with Multiple Steroid Receptor Response Elements

The specification complies with 35 U.S.C. §112 because it provides adequate description as to how any mammalian cell with multiple steroid receptor elements can be used for the method of the claimed invention for the following reasons.

The requirements of 35 U.S.C. §112, first paragraph, are fulfilled where one skilled in the art could use the invention, given the specification disclosure, without undue experimentation[1]. Undue breadth is analyzed in terms of whether it would have involved undue experimentation to achieve the claimed invention. The determination of what constitutes undue experimentation in a given case, requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art[2].

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed[3].

In *Ex parte Forman*, the Board set forth the following criteria for undue experimentation:

> The question of undue breadth is analyzed in the view of:
>
> (1) the quantity of experimentation necessary,
>
> (2) the amount of direction or guidance presented,

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[1] *In Re Eynde*, 480 F2d 1364, 178 USPQ 470 (CCPA 1970)

[2] *Ex parte Forman, et al.*, 230 USPQ 546, 547 (BPAI 1986).

[3] *Ex parte Forman, et al.*, 230 USPQ 546, 547 (BPAI 1986).

(3) the presence or absence of working examples,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the relative skill of those in that art, and

(7) the unpredictability of the art[4].

The unpredictability of the art is only one factor that must be evaluated and weighed with the other factors.

The specification fully enable the use of any mammalian cell with multiple steroid receptor response elements in the claimed methods, namely, how to screen for a ligand that activates the translocation of a steroid receptor to the nucleus in a mammalian cell, because of the following reasons.

1. The steroid hormone signal transduction pathway is conserved in all eukaryotic cells, including mammalian cells. Translocation or movement of a steroid receptor from the cytoplasm to the cell nucleus is a necessary step for steroid receptors to modulate steroid hormone-responsive gene expression by steroid hormones. The Applicants have demonstrated translocation of the steroid receptor to the nucleus of a mammalian cell (in the specification at page 47, line 1 to page 48, line 14) as part of a screening assay to find ligands that activate the translocation of a steroid receptor to the nucleus in a mammalian cell. In one embodiment, the ligand is dexamethasone and a dose response curve for dexamethasone is provided (in the specification at page 47, lines 1-8). In another embodiment, the ligand is RU486 (in the specification at page 47, lines 26-27; page 48, lines 2-4). In yet another embodiment, the ligand is progesterone (in the specification at page 48, lines 5-7). When a non-ligand for a particular receptor is used to treat a fluorescent receptor, no translocation is observed, demonstrating importance of activating the steroid

receptor for translocation to occur from cytoplasm to the nucleus (in the specification at page 48, lines 7-8).

2. The specification provides adequate written description of examples of steroid response elements in an array. For example, the steroid nuclear receptor can be ER, AR, GR, PR, and/or MR (in the specification at page 12, line 19; page 13, line 11; page 18, lines 1-4; page 56, lines 9-17). With regard to ER, Applicants teach the sequence of the steroid response element in the specification at page 59, lines 4-5 and lines 15-17 and methods for making it in the specification at page 59, lines 4-21. With regard to GR, Applicants teach the sequence of the steroid response element in the specification at page 59, lines 3-4 and lines 10-14 and methods for making it in the specification at page 59, lines 3-21. With regard to AR, PR, and MR, the consensus sequence of each of these steroid response elements are the same, and each receptor can bind to the steroid hormone-responsive elements that are recognized by GR.

Hence, no undue experimentation would be required to practice the claimed invention. Accordingly, Applicants respectfully request that the Office withdraw the rejection.

CONCLUSION

Applicants submit that the standards for written description under 35 U.S.C. §112, first paragraph, have been met in view of Applicants' teaching in the specification.

Applicants respectfully request withdrawal of the 35 U.S.C. §112 rejection.

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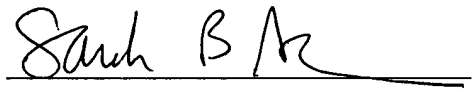
[4] *Forman* at page 547, supra.

No fees, other than the fees for filing the Appeal Brief and the extension of time fees, are deemed necessary in connection with the filing of this Appeal Brief. If any further fees are necessary, the Patent Office is authorized to charge any additional fees to Deposit Account No. 50-0306.

Respectfully submitted,



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APPENDIX A
(pending and entered claims as of September 18, 2006)

1 to 15. (Cancelled)

16. (Previously presented) A method of screening for a ligand that activates the translocation of a steroid receptor to the nucleus in a mammalian cell comprising:

a. contacting a mammalian cell having a nucleus with the ligand, wherein the cell has a plurality of steroid receptor response elements, wherein the steroid receptor response elements comprise a plurality of AGAACA (SEQ ID NO:4) or AGGTCA (SEQ ID NO:5), in an array such that the response element can be directly detected when bound by fluorescently labeled steroid receptor; and

b. detecting the location of fluorescence within the cell,

a change in the relative fluorescence of the nucleus to the cytoplasm so as to increase the fluorescence of the nucleus indicating a ligand that activates the translocation of a steroid receptor to the nucleus in a mammalian cell.

17. (Original) The method of claim 16, wherein the fluorescently labeled steroid receptor is fluorescently labeled with a green fluorescent protein.

18. (Previously presented) A method of screening for a ligand that activates the translocation of a steroid receptor to the nucleus in a mammalian cell comprising:

a. contacting a mammalian cell having a nucleus with the ligand, wherein the cell has a plurality of steroid receptor response elements, wherein the steroid receptor response elements comprise a plurality of AGAACA (SEQ ID NO:4) or AGGTCA (SEQ ID NO:5), in an array such that the response element can be directly detected when bound by fluorescently labeled steroid receptor; and

b. detecting the location of fluorescence within the cell,

a change in the relative fluorescence of the nucleus to the cytoplasm so as to increase the fluorescence of the nucleus indicating a ligand that activates the translocation of a steroid receptor to the nucleus in a mammalian cell,

wherein the mammalian cell is a cell of the cell line designated 3134 deposited with American Type Culture Collection under accession number CRL-11998 (ATCC).

19 to 58. (Cancelled)